Remarks

Claims 1-16, 20, and 22-23 were pending in this application. As described below, claim 20 has been withdrawn without prejudice to prosecution in another application. Accordingly, claims 1-16, and 22-23 are now pending in this application. Claims 8, 9 and 13 have been amended to correct inadvertent typographical errors. In particular, the word "for" has been deleted from claims 8 and 9. The word "modulating," which has antecedent basis in claim 1, has been substituted for "inhibitory" in claim 13. Applicants submit that such amendments do not add new matter to the claims.

Applicants thank the Examiner for the helpful discussion during the telephone interview of February 12, 2003. As agreed upon during the interview, Applicants agree to withdraw kit claim 20 without prejudice so that, as stated by the Examiner, pending claims 1-16 and 22-23 will be allowed. Pursuant to this agreement, Applicants provide a further explanation of the differences between the prior art and the invention as follows.

The Examiner has rejected claims 1-16, 20 and 22-23 under 35 U.S.C. § 102(a) alleging that Lynch et al. (U.S. Patent 5,998,152) anticipates the claimed assay for nucleic acid religation (citing *inter alia* col. 19, lines 32-60). While applicant maintains that the methods and kits of the invention are novel and are not anticipated by the Lynch et al. reference, claim 20 has been canceled without prejudice to expedite the prosecution of this application. Applicants respectfully traverse this rejection as follows.

Claim 1 provides to a high-throughput method of screening compounds capable of modulating topoisomerase activity comprising, incubating at least a first nucleic acid, a topoisomerase and a potential topoisomerase-modulating compound, wherein the nucleic acid comprises at least one tag, and assaying for a nucleic acid religation product.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference

between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Applicants submit that while the invention is directed to topoisomerase assays involving detection of a religation product, the assays of Lynch et al. rely upon detecting a cleaved DNA that is formed by the topoisomerase. See, e.g., U.S. Patent 5,998,152 Figures 1-4. While topoisomerases can cleave and subsequently ligate nucleic acids (see, e.g., U.S. Patent 5,998,152, col. 5, lines 19-67) Lynch et al. chose to detect only the cleavage product and not the ligation product generated by topoisomerases. For example, in the liquid phase assays described in Lynch et al. at column 19, two labels present on a substrate nucleic acid are positioned in proximity such that emission from one of the labels is quenched by the proximity of the other label. A detectable emission signal is generated as a topoisomerase cleaves the nucleic acid substrate and the two labels become separated. If the nucleic acid were to be religated, the two labels would come into proximity and the signal would be quenched. Hence, religation of a cleaved nucleic acid would effectively lead to no signal, and return the nucleic acid to the same undetectable state it was in prior to treatment with the topoisomerase. Applicants submit that such cleavage and re-ligation could not be distinguished from the absence of any topoisomerase activity on the original nucleic acid substrate. Thus, these assays by Lynch et al. do not anticipate the claimed invention because they do not permit detection of re-ligation.

In solid phase assays described by Lynch et al., a topoisomerase-nucleic acid cleavage complex is trapped on a solid substrate. Only this complex is detected, and no other, because a tag on the nucleic acid substrate is used to capture the complex on the solid substrate and an epitope on the topoisomerase is detected. See, e.g., U.S. Patent 5,998,152 Figure 1. In an alternate assay, the complex is captured through an epitope on the enzyme and the nucleic acid is detected. See, e.g., U.S. Patent 5,998,152, Figure 3. Hence, the presence of both the cleaved nucleic acid and the topoisomerase is needed or no signal will be detected. Moreover, the assay of Lynch et al. employs a denaturant that is specifically designed to prevent "reversal" or religation of the cleaved DNA. See, e.g., U.S. Patent 5,998,152, Col. 4, Line 63 to Col. 5, Line2;

Figures 1-4. After denaturation, such a denatured topoisomerase could not catalyze any ligation step. Hence, not only does Lynch et al. fail to disclose the step of detecting nucleic acid religation, assays carried out according to Lynch et al. render religation an impossibility.

The Examiner has also asserted that Lynch et al. describe a second nucleic acid that is a religation strand, comprising oligonucleotides operatively associated with a marker tag (citing col. 5, lines 6-67 and Figures 1-4). Official Action mailed Dec. 10, 2002 at page 3. However, this text of the Lynch et al. patent merely provides a background on topoisomerases and does not disclose or teach labeling or marking a religation strand so that is can be separately detected after cleavage and ligation by a topoisomerase.

The Examiner further asserts that Lynch et al. describe incubating a first and a second nucleic acid (citing col. 19, lines 25-32, Examples 1-3 and Figures 1-4). However, the text at col. 19, lines 25-32 merely discloses substrate nucleic acids, each having both a first label and a second label that are used in the liquid phase assay described above where separation of the labels upon cleavage gives rise to a signal. Similarly, the Examiner's allegations that Lynch et al. teach an assay method that comprises measuring the level of nucleic acid religation activity in the presence and absence of the topoisomerase modulating compound (citing col. 19, line 25 to col. 21, line 16) are also unfounded, because this portion of the Lynch et al. patent merely describes the liquid phase assay involving detection of an unquenched signal generated by separation of the labels upon cleavage of a doubly labeled DNA substrate.

The Examiner has also asserted that Lynch et al. describe a first nucleic acid operatively associated with an affinity tag and a second nucleic acid that is operatively associated with a detection tag (citing col. 14, line 30 to col. 16, line 13). See Official Action mailed Dec. 10, 2002 at page 3. However, the text at col. 14, line 30 to col. 16, line 13 merely discloses labels to detect a nucleic acid cleaved by a topoisomerase and not two distinctly labeled nucleic acids. In fact Lynch et al. does not disclose or suggest any assay that involves ligating a first and a second nucleic acid by a topoisomerase.

In conclusion, Lynch et al. disclose assays for detecting cleavage, not religation, by a topoisomerase. Hence, Lynch et al. does not anticipate the claimed subject matter, and Applicants respectfully request withdrawal of this rejection of the claims under 35 U.S.C. § 102(a).

Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney (516-795-6820) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: *The undersigned hereby certifies that this correspondence is being deposited with the United States Postal* Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 5th day of March, 2003.

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Name

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Signature